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Asthma, Sulfur Dioxide and the Clean Air Act

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr, Professor of Medicine, and James L. Naughton, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR. SMITH:* *This Medical Staff Conference will be concerned with our chemical environment and the public policies designed to control that environment in a manner consistent with human health. The topic will be "Asthma, Sulfur Dioxide and the Clean Air Act." Dr. Homer Boushey will give the presentation.*

DR. BOUSHEY:† In my discussion I shall relate the findings of our laboratory on the effects of sulfur dioxide (SO_2) in patients with asthma, first to theories about the mechanisms of bronchial hyperreactivity, an abnormality that may be fundamental to the pathogenesis of asthma and then to questions of national policy on air quality. I plan also to review briefly some of the epidemiologic data that suggest a relationship between levels of sulfur dioxide and particulates in the air and respiratory disease, and finally to explain the controversy over how the Clean Air Act of 1970 should be amended before it is reauthorized.

Historical Background

Historically, the clearest evidence for a relationship between levels of sulfur dioxide and particulates and death was made apparent by a number of acute air pollution crises in which meteorologic conditions resulted in stagnation of air and pronounced increases in the level of air pollutants. The first of these to be recognized occurred in the Meuse Valley in Belgium in the mid-1930's.[1] Another occurred in this country in Donora, Pennsylvania, in 1948,[2] but the most dramatic of the acute episodes occurred in London in December 1952.[3] An unusually dense smog rich in sulfur dioxide and particulates enveloped virtually the whole of Greater London from Friday through Tuesday morning. Over the days of the smog and the two weeks thereafter, the death rate in Greater London achieved a level that had rarely been exceeded in the previous 100 years, for example, at the height of the cholera epidemic of 1854, and of the influenza epidemic of 1918-1919. Comparison of mortality during the crisis with mortality in the previous weeks and with the same period in the previous year showed that there were between 4,000 and 8,000 more deaths than usual in London over 11 days. Most of these deaths were attributed to respiratory diseases—pneumonia, bronchitis, lung cancer, asthma or "other respiratory diseases." The increase in mortality was greatest in infants and elderly people,

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ABBREVIATIONS USED IN TEXT

EPA = Environmental Protection Agency
ppm = parts per million

but mortality was also increased in young adults and adolescents.

The observed relationship between levels of sulfur dioxide and particulates and excess mortality during acute air pollution crises led to investigations of the relationship between daily mortality and levels of these pollutants. Studies from many different countries have shown a similar trend of higher mortality on days with greater air pollution. One study in New York, for example, correlated deaths from all reported causes on a daily basis from 1962 through 1966 with the levels of sulfur dioxide and particulates measured in Upper Manhattan.[4] After death rates were adjusted for seasonal cycles, temperature, influenza epidemics, holidays and so forth, they significantly correlated with levels of sulfur dioxide. Mortality was 2 percent greater than predicted on days when sulfur dioxide exceeded 0.19 parts per million (ppm), and was 1.5 percent less than predicted on days when sulfur dioxide was less than 0.01 ppm. These data do not specifically incriminate sulfur dioxide as responsible for the increase in mortality, for sulfur dioxide levels are usually paralleled by levels of particulates. It is possible that particulate matter or some other copollutant, rather than sulfur dioxide itself, is responsible for the differences in mortality.

Other epidemiologic studies have shown that levels of sulfur dioxide and particulates also correlate with the prevalence of chronic respiratory disease. The symptoms of persistent cough and sputum production in adults and the incidence of premature retirement or death from bronchitis have been found to be greater in areas with higher levels of sulfur dioxide and particulates, even when differences in social class and smoking habits are taken into account.[5] These differences are widened between smokers and nonsmokers as air pollution increases, suggesting some synergism between air pollution and cigarette smoking in producing chronic obstructive pulmonary disease. The findings of studies in children are similar; the incidence of infections of the lower respiratory tract correlates with residence in areas of greater air pollution.[6] This may be particularly important, for other epidemiologic studies show that the incidence of obstructive ventilatory defects in adults correlates with the history of lower respiratory tract infections in childhood.

Epidemiologists appear to have been quicker than clinical physiologists or toxicologists in recognizing that people with asthma may represent a subsegment of the population particularly sensitive to sulfur dioxide. In the episode in Donora, for example, 88 percent of the people with asthma complained of marked respiratory symptoms; only 43 percent of the general population had similar complaints. Subsequent studies have shown that the frequency of emergency room visits for asthmatic complaints correlates with atmospheric levels of sulfur dioxide.[7] Zeidberg and co-workers[8] similarly found a direct correlation between the severity of asthmatic symptoms as inferred from diaries kept by asthmatic patients and the atmospheric levels of sulfur dioxide. This finding is remarkable because the levels of sulfur dioxide in Nashville, where the study was done, were lower than in larger industrial cities of the Northeast and Midwest of this country.

Despite these provocative epidemiologic studies, one must be cautious in attributing worsening of asthmatic symptoms to levels of a particular pollutant. Not only is sulfur dioxide ordinarily present with other pollutants, especially particulates, but other atmospheric variables such as air temperature or humidity might also have interacted with sulfur dioxide or a copollutant in producing the symptoms. Another problem is that asthmatic symptoms may be provoked by a wide variety of agents and events. The amount of dust or pollens in the air might have increased, for example, during the thermal inversions that resulted in higher levels of sulfur dioxide. The epidemiologic studies can therefore provide suggestive circumstantial evidence but do not pinpoint sulfur dioxide as the cause of the worsening of asthmatic symptoms. For this reason, laboratory studies of the effects of a single pollutant on pulmonary function are important. For sulfur dioxide, such studies showed little response in healthy people exposed to concentrations below 5 ppm, a high level of sulfur dioxide. Frank and associates[9] exposed 11 healthy adults to 1, 5 and 13 ppm of sulfur dioxide and found no change in the mean value for airway resistance after exposure to 1 ppm, a level infrequently exceeded in most American cities. They found significant increases in resistance on exposure to 5 and 13 ppm, but these levels are achieved only in certain occupational settings, not in the general atmosphere. Frank and co-workers[9] did find, however, that one of their subjects had considerable bronchospasm on inhaling 1 ppm, and they remarked that this person's history of wheezing with viral infections suggested that he might have had an asthmatic predisposition. Their study is typical of many studies done in the 1960's; that is, in groups of healthy adult volunteers who were exposed to sulfur dioxide, no changes in maximal expiratory flow or in airway resistance were found in the group as a whole with exposure to levels of sulfur dioxide below 5 ppm. In some people, however, many of whom were reported to have occasional asthmatic symptoms, substantial responses occurred with exposure to much lower levels (such as 1 ppm). Despite these observations, the first study of a group of asthmatic subjects was not undertaken until 1980 when Sheppard, Wong, Uehara and others in our laboratory[10] investigated the effects of SO_2 in people with asthma.

Effects on Persons With Asthma

Our work was not provoked so much by curiosity over the disparity between the results of the epidemiologic studies, which suggested a strong relationship between low levels of sulfur dioxide and asthmatic symptoms, and the results of controlled exposure studies, which showed no effect of levels below 5 ppm except in an occasional and possibly random individual. Rather, our investigation was spurred by our interest in the mechanism of bronchial hyperreactivity. It has long been known that patients with asthma will have intense, symptomatic bronchospasm on inhaling levels of histamine or methacholine so small as to cause no measurable effect in normal people. This abnormal responsiveness of the airways is referred to as bronchial hyperreactivity; it is ubiquitous in people with asthma and the degree of bronchial hyperreactivity correlates with the clinical severity of asthma as estimated by symptom scores or medication requirements. Furthermore, the events that increase bronchial reactivity, such as viral infections and exposure to oxidizing pollutants, also increase the clinical severity of asthma. There is now a widespread consensus among investigators that bronchial hyperreactivity is somehow fundamental to the pathogenesis of asthma; that is, asthma may require not just the release of the chemical mediators of anaphylaxis, but also an exaggeration of the responsiveness of the pulmonary system to their effects.[11] Despite the consensus about the importance of bronchial hyperreactivity, there is little agreement as to its underlying mechanisms. The hypothesis we favor is that bronchial hyperreactivity is due to an exaggeration of reflex responsiveness to inhaled materials (Figure 1).

Evidence supporting this hypothesis was initially provided by studies in dogs, in which cutting the vagus nerves greatly reduced the response to inhaled or injected histamine.[12] It was later shown that in people with asthma or chronic bronchitis, pretreatment with atropine sulfate (a postganglionic cholinergic antagonist that has no effect on the response of smooth muscle to histamine in vitro) blocked the response to subsequent inhalation of histamine.[13] This finding suggests that the exaggerated response to histamine associated with asthma is mediated through parasympathetic pathways, but it does not identify the site of altered function within the pathway. Holtzman

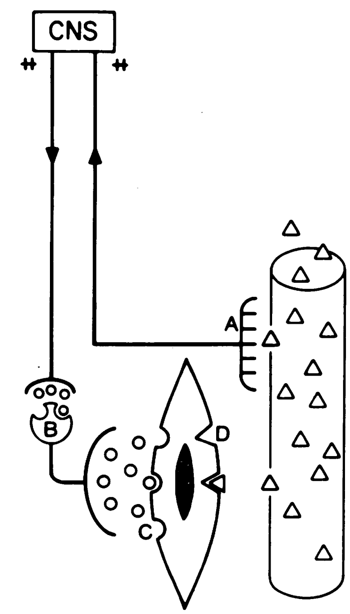

Figure 1.—Conceptual model of mechanisms of response to inhaled irritants. The airway is represented by a hollow cylinder with branching vagal sensory endings (A) lying adjacent to the lumen. Afferent pathways in the vagus nerves travel to the central nervous system (CNS); efferent pathways from the CNS travel to efferent ganglia (B). Postganglionic fibers release acetylcholine (o), which binds to muscarinic receptors (C) on airway smooth muscle. Inhaled histamine (Δ) normally causes bronchoconstriction by two mechanisms: it diffuses across the airway epithelium and binds to histamine receptors (D) on smooth muscle, provoking contraction; histamine also stimulates vagal sensory endings causing reflex release of acetylcholine at the postganglionic nerve endings and further provoking muscle contraction. (Adapted from Holtzman et al.[14])

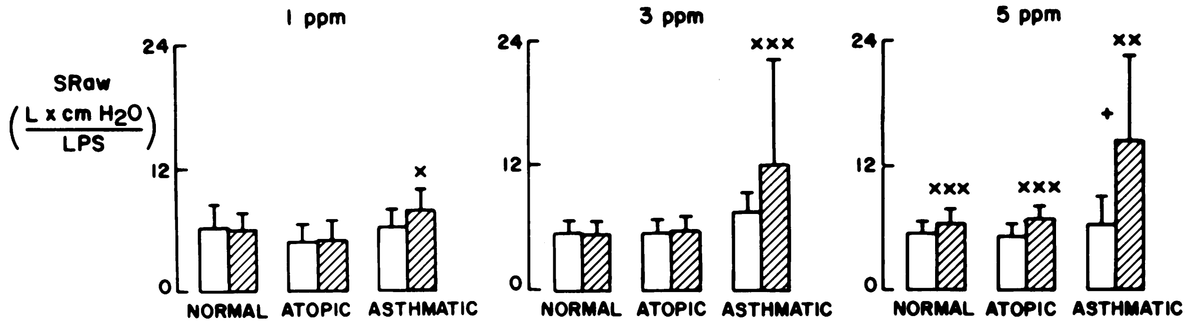

Figure 2.—Specific airway resistance (SRaw) after 5 min of breathing filtered air (□) and during the last 5 min of exposure (▨) to 1, 3 and 5 ppm of sulfur dioxide in normal, atopic and asthmatic subjects. Data are mean ± standard deviation; n = 7 except for asthmatic subjects breathing 5 ppm; in this group, n = 6. x, xx, xxx significantly different from value after exposure to air—$P<0.05$, 0.025, and 0.01, respectively; increase in SRaw significantly greater in asthmatic group—$P<0.005$. Units L × cm H_2O/LPS refers to liters of lung volume times airway resistance (cm H_2O/liters per second). (Reproduced with permission from Sheppard et al.[10])

and co-workers[14] have since found that pretreatment with aerosolized hexamethonium, a ganglion-blocking agent, also blocked the response to inhaled histamine. Hexamethonium did not, however, alter the response to inhaled methacholine, a drug that acts directly at muscarinic receptor sites. This finding suggests that bronchial hyperreactivity is due to a difference in activity distal to the ganglion, possibly in the number or binding affinity of muscarinic receptors on bronchial smooth muscle. If this hypothesis is correct, any agent that acts uniquely through reflex pathways should cause exaggerated bronchoconstriction in people with bronchial hyperreactivity. Sulfur dioxide appears to be such an agent. Nadel and associates[15] have shown in cats that the insufflation of sulfur dioxide into the isolated upper airway caused constriction of both upper and lower airways; the converse was also true: insufflation of sulfur dioxide into the lower airways caused upper airway contraction. These responses were further shown to depend on innervation of the larynx and tracheobronchial tree; sulfur dioxide had little direct effect on smooth muscle.

As a test of our hypothesis on the mechanism underlying bronchial hyperreactivity, we predicted that people with asthma should be abnormally sensitive to sulfur dioxide. Accordingly, we studied seven healthy people, seven people with atopic disease—usually allergic rhinitis, but without asthma—and seven with mild asthma.[10] Each person was exposed for ten minutes to 1, 3, or 5 ppm of sulfur dioxide while breathing through a mouthpiece. In the asthmatic persons specific airway resistance increased significantly after inhaling each level of sulfur dioxide, and the magnitude of the response was related to the concentration inhaled (Figure 2). The response of the asthmatic persons was significantly greater than those of the atopic and healthy control subjects. Two of the people with asthma complained of wheezing and shortness of breath on inhaling 1 ppm; four of six complained of wheezing and shortness of breath on inhaling 5 ppm. In some subjects, the response was dramatic even at 3 ppm (Figure 3). Pretreatment with aerosolized atropine sulfate blocked the response to sulfur dioxide in all subjects. Thus, our study showed that people with asthma responded to lower levels of sulfur dioxide and with greater bronchoconstriction than people without asthma.

Because atmospheric levels of sulfur dioxide rarely exceed 1 ppm in American cities, the relevance of our findings to normal living conditions

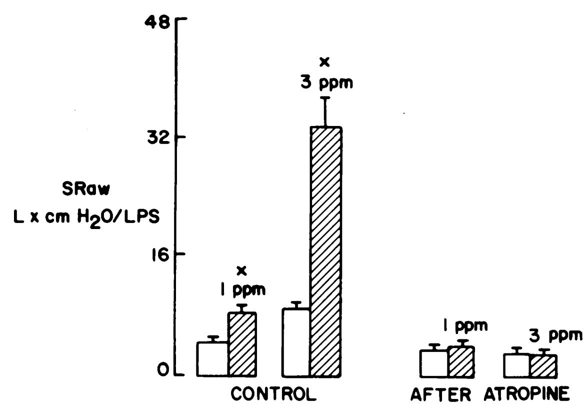

Figure 3.—Specific airway resistance (SRaw) after 5 min of breathing filtered air (□) and during the last 5 min of exposure to 1 and 3 ppm of sulfur dioxide (▨) in the control state and after treatment with atropine sulfate in one asthmatic subject. Data are mean ± SD; x significantly different from value after exposure to air—$P<0.0005$. Units L × cm H_2O/LPS refers to liters of lung volume times airway resistance (cm H_2O/liters per second). (Reproduced with permission from Sheppard et al.[10])

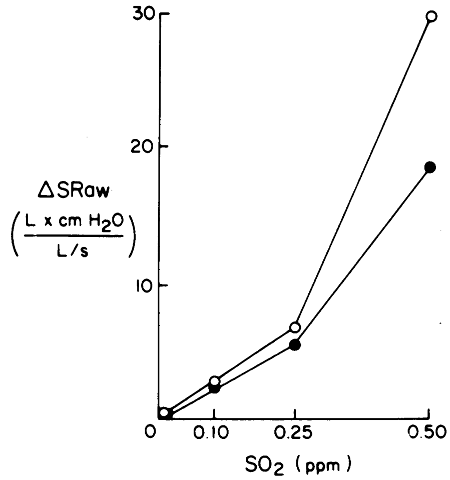

Figure 4.—Dose-response to sulfur dioxide (SO_2) inhaled during exercise in two subjects (● and o). The ΔSRaw is the difference between baseline specific airway resistance and specific airway resistance after inhalation of SO_2. (Reproduced with permission from Sheppard et al.[16])

could be questioned, but they are clearly relevant to the work place, where the permitted level of sulfur dioxide is 5 ppm in a time-weighted average over eight hours. Sulfur dioxide levels are therefore permitted to be much higher than 5 ppm for short periods of time without violating the Occupational Safety and Health Administration (OSHA) standard.

The finding that people with asthma also develop bronchoconstriction on inhaling lower concentrations of SO_2 was made by Sheppard and co-workers[16] who remarked that in the first study, all subjects were exposed to SO_2 while seated and at rest. Sulfur dioxide is a highly soluble gas and is well absorbed by the mucosa of upper airways. Only a small proportion of the concentrations entering the mouth travels below the larynx. Sheppard predicted that with the increase in both inspiratory flow and volume required for exercise, a greater proportion of inhaled SO_2 would reach the larynx and tracheobronchial tree, and more pronounced responses would result. Sheppard's study of the interaction of exercise and sulfur dioxide in seven people with very mild asthma confirmed this prediction.[16] Neither inhalation of 0.5 ppm of sulfur dioxide at rest, nor moderate exercise (400 kilopond-meters per minute) while breathing humidified filtered air caused an increase in specific resistance. At the same level of exercise while breathing 0.5 ppm of sulfur dioxide, however, specific airway resistance increased strikingly, and several subjects complained of chest tightness and shortness of breath. When the same people were challenged with 0.25 ppm of sulfur dioxide, a small but statistically significant increase in specific resistance persisted. In the two most sensitive persons, inhalation of as little as 0.1 ppm of SO_2 during moderate exercise caused a small but significant increase in specific airway resistance (Figure 4). This demonstrates that very low levels of sulfur dioxide inhaled during exercise can cause bronchospasm in people with asthma.

Our findings that the airways of people with asthma are sensitive to sulfur dioxide and that exercise potentiates the responsiveness have been confirmed by investigators at the University of Washington using slightly different methods. Koenig and co-workers[17] have reported that adolescents with asthma and children with hay fever are more sensitive to sulfur dioxide, and that this sensitivity is potentiated by exercise.

With respect to our understanding of the mechanisms of bronchial hyperreactivity, these findings represent a small but satisfying step forward. They also have important implications with respect to the regulation of ambient air quality in the United States. Sulfur dioxide is produced by any industry using petrochemicals as a source of power. The principal sources of sulfur dioxide in the US are refineries, foundries and any other industries that generate electrical power by burning oil or coal. America has been described as the Saudi Arabia of coal, and increased use of coal has been advocated as a way of reducing our dependency on imported oil. Our coal is rich in sulfur and is therefore a potential source of large quantities of sulfur dioxide in the next 25 to 50 years.

Clean Air Act

A review of the provisions of the current Clean Air Act will explain why our findings are considered important by both regulatory agencies and industries that generate sulfur dioxide. The original Clean Air Act of 1963 and the Air Quality Act of 1967 both suffered from the same deficiency—they relied on voluntary cooperation by individual states. The states were reluctant to be the first to set stringent standards for fear that they would then be put in a noncompetitive position for attracting industry. The Clean Air Act amendments of 1970 were especially important in that they established the first comprehensive program for attacking air pollution nationwide. Several very important features were included in these amendments. One feature was to establish the Environmental Protection Agency (EPA), which was required to set national air-quality standards that were to be attained by 1975. States were charged with developing plans for achieving these standards, and the plans were subject to the EPA's approval. These plans differed in states with different problems. In the industrial Northeast, for example, the plans involved modifying existing industrial plants so that the quantity of pollutants emitted would be reduced. In California where photochemical pollution is a greater problem, the plans included setting tougher standards for automobile emissions. The Clean Air Act amendments also specified that the EPA was authorized to set emission limits for new sources of pollutants in any part of the country. As the result of this provision, new power plants generate only 12 lb (5.4 kg) of sulfur dioxide per ton (907 kg) of coal consumed, whereas old plants generate as much as 83 lb (38 kg) per ton of coal—a sevenfold difference. Other standards have resulted in substantial reductions in hydrocarbons, nitrogen oxide and carbon monoxide from automobiles. The EPA was additionally authorized to levy fines on industries that failed to comply with its directives, and the fines were to be sufficiently great to offset whatever economic advantage an industry may have gained by failing to comply to the Clean Air Act. States and even individual citizen groups may bring civil action against polluters, providing further impetus for enforcement.

By developing a comprehensive plan for controlling pollution, and by granting specific, effective enforcement powers, the Clean Air Act amendments of 1970 have resulted in improvement in air quality, especially for the pollutants specified in the Clean Air Act as requiring regulation ("criteria pollutants"). The procedure that is followed in establishing a national standard for a pollutant is as follows: first, the EPA prepares a criteria document summarizing the epidemiologic, toxicologic and clinical studies that are relevant to that agent. Once the criteria document has been reviewed by invited consultants, the EPA administrator then publicizes the document, proposes standards for the pollutant and invites response from the public. After the public has had a chance to respond and the proposals have been reviewed by an independent advisory committee, the final promulgation of standards is made.

The law requires that the primary standards for a pollutant protect sensitive groups of the population against adverse health effects and that the standards ensure a margin of safety between the "probable effects level" and the level permitted. The standard is to be defined on the basis of health alone; consideration of the cost of achieving standards is not permitted. The standards for sulfur dioxide are that the average level of sulfur dioxide over 24 hours not exceed 0.14 ppm on more than one day each year, and that the average annual concentration not exceed 0.03 ppm. There is no short-term standard for sulfur dioxide, and the 24-hour standard of 0.14 ppm means that the level could be very much higher for short periods as long as the level was much lower at other times in the day. If, for example, sulfur dioxide levels were low throughout the night, the average daily level might remain below 0.14 ppm despite quite high levels of SO_2 during working hours. Our finding that people with mild asthma may develop bronchospasm on inhaling sulfur dioxide for five minutes suggests that under the provisions of the current law, a short-term standard is required if sensitive groups are to be protected with a margin of safety.

Spokesmen for industries and independent investigators have disputed the relevance of these findings to what they call "real life" conditions. One of the criticisms of our work, for example, is that our subjects breathed through a mouthpiece during their exposure to sulfur dioxide, bypassing the important defensive functions of the nose.[18] It is argued that our findings may therefore be considered irrelevant to environmental standards for sulfur dioxide. This particular criticism is specious because with viral rhinitis or any of the common causes of nasal obstruction, most ventilation must pass through the mouth. People with asthma often also have allergic rhinitis and therefore have a higher incidence of nasal obstruction. Furthermore, ventilation shifts from being predominately nasal to oronasal with exercise, increasing the proportion of ventilation that bypasses the nose. Kirkpatrick and associates[19] directly investigated the importance of the defensive role of the nose by comparing the response of people with asthma who were exposed to sulfur dioxide while wearing a face mask that permitted breathing through both the nose and the mouth to the response in the same subjects exposed while breathing through the mouth alone. The response was only slightly lessened when his subjects breathed through the face mask, and symptomatic bronchospasm still occurred on inhaling 0.5 ppm of sulfur dioxide during light exercise.

Another approach to dealing with data such as ours is to change the law. The Business Round Table, a group of industrial representatives, has proposed that the definition of adverse health effects be changed to "a permanent or incapacitating illness." This change in definition would mean that transient, distressing, but not incapacitating, bronchospasm would not be considered relevant to standards for sulfur dioxide. Another proposal is that the requirements to protect sensitive groups be eliminated because a few individuals abnormally sensitive to almost any material can be found in a nation of 250 million people. The Business Round Table further proposes that the concepts of "probable effect levels" and of "a margin of safety" be replaced with the concept of "acceptable risk," and that the definition of what is an acceptable risk be made with consideration of the costs of achieving standards. A problem with this proposal is that it is difficult to determine the costs of achieving a standard because estimates of cost are based on available technology and until the passage of the amendments in 1970, there was virtually no incentive for developing technology to reduce the emission of pollutants economically. Considering costs also requires that some dollar value be ascribed to suffering, and suffering is disproportionately shared. That is, sensitive groups may suffer marked distress while the rest of us notice no effect.

A final approach to dealing with data showing adverse health effects from atmospheric pollution is to change the personnel responsible for enforcing the Clean Air Act. The San Francisco *Examiner* recently reported that of the 15 people appointed to the Environmental Protection Agency by the Reagan administration, 11 have worked for the industries that the EPA regulates, such as the steel, paper and chemical industries. The public has cause to worry that this change in the personnel responsible for enforcing air-quality standards may severely threaten the progress this nation has made in cleaning its air and may prevent any further progress in dealing with other potentially serious problems, such as the acidification of our lakes and waterways by acid rain.

Conclusion

Our work has shown that people with asthma are abnormally sensitive to inhalation of sulfur dioxide and that bronchospasm may develop if they pursue activities that require light exercise while breathing air containing a level of sulfur dioxide permitted by current ambient air-quality standards. The provisions of the Clean Air Act of 1970 require that sensitive groups in the population be protected against adverse health effects, and our data therefore indicate the need for a short-term standard for sulfur dioxide. The cost of attaining such a standard is unknown. In any case, under current law cost is irrelevant to the process of setting standards; consideration of cost is permitted only in designing plans for achieving standards.

The decision as to whether the health of sensitive subgroups in our population should continue to be protected is an important one. This decision should be made only after the issue has been explicitly stated for discussion and debate by the American public.

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